

Applicants respectfully request that the submission of a clean claim set establishes the current claim set, and obviates the issue of amended *versus* non-amended claims.

2. Applicants acknowledge the Office's notice of sequence compliance for the instant application.

3. Applicants acknowledge the cancellation of claims 59-60, 65, 67, 71, 77, and 79-82.

4. The Title stands objected to for failing to accurately describe the claimed invention.

Applicants request that the objection to the Title be withdrawn in light of the newly submitted title *supra*.

5. The specification stands objected to under 37 CFR 1.821(d) because SEQ ID NOS were not disclosed in the specification adjacent referenced sequences (e.g. pages 32-33).

Applicants have reviewed the entire specification and have amended pages 32-33 to include the sequence identifiers next to the appropriate sequences. Therefore, Applicants respectfully request that the objection to the specification withdrawn, and believe that the entire specification is now in compliance with 37 CFR 1.821(d).

6. Claim 64 and 86 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicants request that the objection to previous claims 64 and 86 under 37 CFR 1.75(c) be withdrawn in light of the new claim set in which the claims drawn to antibodies conjugated to a detectable label are independently recited.

7. Claim 68 is objected to for the following informality: "p16Kd" should be "16 kD".

Applicants request that the objection to previous claim 68 be withdrawn, as all instances of "p16 kD" have been amended to recite -- 16 kD --. Applicants submit that the scope of this claim is not narrowed by this amendment.

8. Claims 76 and 90 are objected to because of the following informalities: it appears the last phrase of each claim was intended to read -- in samples of cells --.

Applicants request that the objection to claims previous claims 76 and 90 be withdrawn as the newly submitted claims recite -- in samples of cells --. Applicants submit that the scope of these claims is not narrowed by this amendment.

9. Claims 68, 70, and 87-88 are objected to because of the following informalities: an article appears to be missing before the word "means".

Applicant has amended the relevant claim set to recite either -- *a* means for detection --, and -- *the* means -- as suggested by the Examiner. Applicants submit that the scope of these claims is not narrowed by this amendment.

35 U.S.C. 112, first paragraph – New Matter, Scope of Enablement, and Written Description

10. Applicants acknowledge the withdrawal of the New Matter rejection by the Examiner.

11. Claims 83-90 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for and providing written description support for an antibody to a p16 protein comprising SEQ ID NO: 35, was asserted not to reasonably provide enablement or written description support for an antibody to a p16 protein "having an amino acid sequence" of SEQ IDNO: 35. The Examiner's position is that the description of a p16 protein comprising SEQ ID NO: 35 or SEQ ID NO: 2 (SEQ ID NO: 35 with an additional 8 amino acids at the amino terminus) and antibodies to p16 proteins comprising SEQ ID NOS: 2 or 35 cannot support the genus of any "p16 protein" having any "subsequence" of SEQ ID NO: 35 by virtue of the recitation of a p16 protein "having an amino acid sequence" of SEQ ID NO: 35.

Applicants respectfully request that the rejection of previous claims 83-90 (new claims 103-112) under scope of enablement and written description be withdrawn as the claims have been amended to recite -- an antibody to a protein *comprising* SEQ ID NO: 35 -- as suggested by the Examiner. Consequently, Applicants believe that the amendment to the claims meets the requirements of enablement and written description under 35 USC 112, first paragraph.

12. Applicants acknowledge the fulfillment of the deposit requirements for the WI38 cell line available from ATCC(CRL-75) under 35 USC 112, first paragraph.

35 U.S.C. 112, second paragraph

13. Claims 11, 58, 61-64, 66, 68-70, and 72-76 are rejected under 35 USC 112, second paragraph, as being indefinite. Specifically,

A) Claims 11, 58, 61-64, 66, 68-70, and 72-76 are ambiguous in their recitation of “a 16 kD protein” in the absence of an indication of the method and conditions used to assign the molecular weight.

Applicants respectfully submit that the rejection of previous claims 11, 58, 61-64, 66, 68-70, and 72-76 (new claims 91-112) under 35 U.S.C. 112, second paragraph has been obviated by the recitation of the method and conditions used to determine the molecular weight of the p16 protein in the claims. Further, Applicants believe the rejection of previous claims 62-63 and 74-75 is moot in view of the cancellation of said claims.

Support for the method and conditions used to determine the molecular weight of the p16 protein can be found in Examples 1-2 and 5 of the instant specification.

B) Claims 62 and 63 are indefinite in that each is dependent on canceled claims 59 and 60.

Applicants respectfully submit that previous claims 62 and 63 have been canceled, and that the rejection under 35 USC 112, second paragraph is moot. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

C) Claims 72-76 are ambiguous in the recitation of “wherein the antibody” because claim 68, from which these claims depend either directly or indirectly, recites both an anti-CCR antibody and an anti-CDK4 antibody.

Applicants respectfully submit that previous claims 72-76 (new claims 101-102), have been amended to recite the intended antibody (i.e., anti-CCR antibody), and are no longer ambiguous. Further, Applicants believe the rejection of previous claims 74-75 under 35 USC 112, second paragraph is moot in view of the cancellation of said claims.

Support for the p16 antibodies can be found on page 33, paragraph 1 of the instant specification.

14. The applicants respectfully submit that the amendments to the claims do not introduce any New Matter in view of the support provided *supra*.

Effective filing date of the instant claims

15. The following is noted with respect to the effective filing date of the instant claims. The Examiner generated a table documenting support for various terms and aspects of the invention.

A) Applicants acknowledge the Office's receipt of the priority document USSN 07/991,997, filed 12/17/92, and that USSN 08/227,371 was not available to the examiner.

B) Applicants note that on page 6 of the Office Action mailed 06/03/2002 (Paper No. 36), the page number for the *antisera* for the '997 application is missing, and note that the pertinent information can be found on pages 22-23 of the '997 application.

C) Applicants note that in paragraph 2 of page 22 of the '997 application, that agents (e.g., antibodies) which recognize "*different subunits*" (i.e., individual proteins such as p16) can be used in conjunction to determine the presence of interactions among the subunits. Lines 26-30 of the same paragraph discuss an agent which recognizes p21 specifically and which does not interact with other proteins as it could be used in conjunction with agents to cyclins or cyclin kinases. Lines 16-18 of the same paragraph describe agents that bind to p16 (i.e. possess specific reactivity). Lines 31-35 of page 22 and lines 1-10 of page 23 of the '997 application describe *antibodies* that specifically react with compounds of the quaternary complexes (i.e., individual subunits), and methods of generating antisera to said compounds.

Therefore, the priority documents show that Applicants had clearly contemplated antibodies to individual proteins of the complexes (e.g., p16), and specific reactivity to those same proteins. Therefore, Applicants assert that the '997 application clearly provides written support for the claimed invention, and the claims should be given the benefit of the filing date of the '997 application, i.e. 12/17/92.

35 U.S.C. 102

16. Claims 66 and 73 are rejected under 35 USC 102(e) as being anticipated by Kamb et al (U.S. Pat. No. 6,090,578), of record.

Applicants respectfully request that the rejection of claims 66 and 73 under 35 USC 102(e) as being anticipated by Kamb et al. be withdrawn in view of the cancellation of claims directed to a purified polyclonal preparation of antibodies. Applicants have cancelled these claims solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

17. Claims 66 and 73 are rejected under 35 USC 102(e) as being anticipated by Skolnick et al (U.S. Pat. No. 5,624,819), of record.

Applicants respectfully request that the rejection of claims 66 and 73 under 35 USC 102(e) as being anticipated by Skolnick et al. be withdrawn in view of the cancellation of the claims directed to a purified preparation of polyclonal antibodies. Applicants have cancelled these claims solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

18. Applicants acknowledge the withdrawal of the rejection of previous claims 68-70, 72-73, and 76 under 35 USC 102(b) as being anticipated by Busch et al. (U.S. Pat. No. 4,794,077) because previous claim 68 was drawn to an antibody which specifically reacts with a p16 protein, which was not addressed by the Busch et al. patent.

35 U.S.C. 103(a)

19. Claims 11, 58, 61-64, 66, 68-70, 72-76, and 83-90 are rejected under 35 USC 103(a) as being unpatentable over Xiong et al. (Genes & Dev. August 1993; 7: 1572-1583, IDS #EO) in view of Busch et al. (U.S. Pat No 4,794,077, of record).

The Examiner's position is that the '997 application appears to disclose written support for antibodies to the p16-CDK4 *complex*, but not to the individual subunits.

The applicants believe that the rejection of previous claims 62-63 and 74-75 are moot in view of the cancellation of those claims. Applicants have cancelled these claims solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Applicants respectfully traverse this rejection to the extent that is maintained over the effective filing date of the claims drawn to antibodies to p16 discussed *supra*.

Applicants had clearly contemplated antibodies to individual proteins of the complexes (e.g., p16), and specific reactivity to those same proteins. Therefore, the Applicants assert that the '997 application clearly provides written support for the claimed invention, and the claims should be given the benefit of the filing date of the '997 application, i.e., 12/17/92.

Further, the Declaration under 37 CFR 1.132 submitted by inventor David Beach with this response resolves the issue of inventorship of Xiong and Hui, rendering this reference unavailable as prior art against this application.

Consequently, Applicants respectfully request that the rejection of the claims under 35 USC 103(a) be withdrawn.

20. Claims 62-63 and 74-75 are rejected under 35 USC 103(a) over either Kamb (US Pat No. 6,090,578, of record) or Skolnick et al. in view of Owens et al. (J. Immunol. Methods February 1994; 168: 149-165)

Applicants believe that the rejection of previous claims 62-63 and 74-75 under 35 USC 103(a) over either Kamb (US Pat No. 6,090,578, of record) or Skolnick et al. in view of Owens et al. (J. Immunol. Methods February 1994; 168: 149-165) is moot in view of the cancellation of those claims. Applicants respectfully request withdrawal of this rejection. Applicants have cancelled these claims solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully Submitted,



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